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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/919,501	08/28/97	O'GORMAN S	SALK2190

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	21

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/919,501	O'Gorman et al
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *Sep 29, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *12-15, 18-24, 26, 28-32, 34-44, and 46-51* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *12-15, 18-24, 26, 28-32, 34-44, and 46-51* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on 9-29-00, paper number 19, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/909501 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-10, 16, 25, 33 and 45 have been canceled. Claims 46-51 have been added. Claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51 are under consideration in the instant application.

Applicants' arguments filed 9-29-00, paper number 20, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

1. Claim 40 is objected to because of the following informalities: the "second pair of recombination target sites" is listed first and the "first pair of recombination target sites" is recited second. This is confusing. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 12-15, 18-24 and 26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 12-15, 18-24 and 26 encompass human embryonic stem cells. Human beings and human embryos (which includes a 1-cell human embryo) are non-statutory subject matter. See 1077 O.G. 24, April 21, 1987. Modification of the claimed subject matter to a non-human mammalian embryonic stem cell would overcome this rejection. If claims 49-51 are supposed to be directed toward ES cells, claims 49-51 should be amended in a similar manner (see 112/2nd).

Claim Rejections - 35 USC § 112

3. Claims 32, 34-43 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The term "gene segments" (claim 43) and "nucleic acid fragment" (claims 32, 34, 35 and 40) do not have adequate written description. An adequate written description of a gene segments or nucleic acid fragments requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to state fragments or segments of DNA can be used in the instant invention. Thus, claiming DNA segments or

fragments that achieve a result without defining what means will do is not in compliance with the description requirement (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA segments or fragments which provide the means for practicing the invention.

4. Claims 12-15, 18-24, 26, 28-32, 34-44 remain rejected and 46-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse ES cell whose genome comprises a nucleic acid construct comprising a nucleic acid sequence encoding recombinase operatively linked to the MP1 promoter and a method of making a transgenic mouse comprising implanting the mouse ES cells above into a host female such that a transgenic mouse is obtained, wherein said transgenic mouse expresses recombinase in its spermatid to a level that results in recombination in an embryo, does not reasonably provide enablement for any mammalian ES cell, any germline-specific promoter or method of making any transgenic animal or recombinant allele as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification is directed toward ES cells comprising a nucleic acid construct encoding a recombinase gene operatively linked to a germline-specific promoter to conditionally express a gene of interest. The purpose of making such ES cells is to make transgenic mice expressing recombinase in their gametes such that the "marker gene would be excised in at least some of the

progeny of ES cell chimeras" (page 3, line 3) or to "deliver recombined target nucleic acid constructs to the early embryo" (page 3, line 13).

The state of the art at the time of filing was such that the phenotype of transgenic animals was unpredictable due to the unpredictability of transgene expression (Mullins, 1996, J. Clin. Invest., Vol. 98, pages S37-S40; see page S37, column 2, line 7). The transgene may even be expressed but not functional (i.e. "silenced") (see page S37, column 2, line 7). Wall teaches transgene behavior was unpredictable because transgene expression often occurs in unintended tissues or at developmentally incorrect times (Wall, 1997, J. Dairy Science, Vol. 80, pages 2213-2224; see page 2216, column 1, "Transgene expression"). The instant claims relate to expressing recombinase in ES cells; however, if germline-specific recombinase activity were not sufficiently high to mediate recombination, embryos expressing recombinase would be mosaic and not display a mutant phenotype (Lewandoski 1997, Current Biology, Vol. 7, pages 148-151; see page 151, column 1, line 4). Thus, recombinase expression may not alter the phenotype of the animal.

The specification discloses making ProCre transgenic mice by transfecting mouse ES cells with a nucleic acid construct comprising a sequence encoding Cre recombinase operatively linked to the mouse protamine 1 (MP1) promoter (page 19, line 25; page 21, line 3). ProCre transgenic mice were bred with transgenic mice containing a nucleic acid construct comprising a loxP-flanked neomycin resistance gene and the β-gal gene disrupting the RNA polymerase II locus (P2Bc, Figure 1, see also page 22, line 10). ProCre/P2Bc male mice were bred with wild-type female mice resulting a majority of embryos carrying a recombined P2Bc gene, namely P2Br,

which does not have the neomycin resistance gene (page 22, lines 22-30). Note that the specification refers to the results of the experiment in Table 1 on page 22, line 30; however, Table 1 is not present in the instant application. The specification does not teach making ES cells with ProCre and P2Bc or isolating ES cells from ProCre/P2Bc transgenic mice. ProCre males bred with P2Bc females did not result in recombination (page 23, line 17).

Heterozygous ProCre/P2Bc male mice demonstrated expression of P2Br in testes but not in kidney, brain or spleen when tested by Southern Blot analysis (page 24, line 4). However, testes tissue and only one other tissue selected from the group of kidney, brain or spleen was tested in each mouse (page 24, line 1). Upon further investigation, the heterozygous ProCre/P2Bc male mice expressed P2Br in the heart, brain and spleen as determined by a more sensitive PCR method (page 24, line 32; page 25, lines 8-13). Thus, heterozygous ProCre/P2Bc male mice expressed P2Br in testes, heart, brain and spleen.

The specification does not enable any mammalian ES cells, any germline-specific promoter or a method of making any transgenic animal as broadly claimed. The specification does not teach making any ES cells other than mouse ES cells, any germline-specific promoters other than those in mice (page 6, lines 1-12) or any germline-specific promoter that functions in a transgenic mouse to produce germline-specific recombinase expression a mouse other than the MP1 promoter. It is not clear that any of the other germline-specific mouse promoters contemplated on page 6, lines 1-12 would have equivalent function as MP1 in transgenic mice, that MP1 would function in any transgenic animal as broadly claimed or that a oocyte-specific promoter would be

functionally equivalent to the MP1 promoter such that functional expression of recombinase would have occurred to levels that would allow recombination. In fact, the MP1 promoter is not germline-specific because it expresses protein in the heart, brain and spleen. It is not clear from the specification that expression in testes, heart, brain and spleen is "substantially exclusive" as defined in the specification (page 8, lines 15-18).

Given the only disclosed use for the ES cells is to make transgenic animals, the unpredictability in the art regarding how to isolate ES cells from mammals other than mice, the unpredictability in the promoter and gene of interest used to make a phenotype of interest in transgenic animals, the lack of correlation between the MP1 promoter and other germline-specific promoters that would have the ability to obtain spermatid-specific recombinase expression in a transgenic animal, the lack of correlation between the ProCre mouse and any other transgenic mammalian species, taken with the teachings in the specification, it would have required one of skill undue experimentation to determine the parameters required to obtain any mammalian ES cell comprising any germline-specific promoter as broadly claimed such that a transgenic animal with a predictable phenotype could be obtained.

Claims reciting the limitation of an ES cell comprising a nucleic acid sequence encoding recombinase operatively linked to the MP1 promoter and further comprising 1) a nucleic acid fragment flanked by two recombinase target sites, 2) a nucleic acid construct encoding recombinase operatively linked to an inducible promoter or 3) a nucleic acid construct encoding recombinase operatively linked to a tissue-specific promoter are not enabled (claims 13-15, 26,

28-32, 34-43, 46-48). The specification does not teach transfecting any ES cells with two constructs of any kind such that the phenotype of the resulting animal could be determined. The specification does teach isolating male ES cell lines from the ProCre mice and transfecting them with a vector comprising a selectable marker flanked by two loxP sites (page 25, lines 22-34; page 26, lines 1-7). A portion of the transfected ES cells recombined such that the selectable marker was removed in some of the ES cells (page 26, lines 7-26). However, the specification does not teach how to use such ES cells or the phenotype of the resulting transgenic mouse is different than the wild-type. The specification does not provide a use for ES cells or mice expressing a marker gene. The specification also contemplates using an inducible promoter to facilitate temporal control of recombinase expression in ES cells (page 19, line 10). The specification does not teach the phenotype of any transgenic animal obtained using an inducible promoter. Given the unpredictability in the art regarding the phenotype of transgenic animals, the specification does not enable ES cells comprising a nucleic acid sequence encoding recombinase operatively linked to the MP1 promoter and further comprising 1) a nucleic acid fragment flanked by two recombinase target sites, 2) a nucleic acid construct encoding recombinase operatively linked to an inducible promoter or 3) a nucleic acid construct encoding recombinase operatively linked to a tissue-specific promoter as claimed.

The methods of claims 28-32, 34-44 and 46-51 are not enabled because the excision of a selectable marker in an ES cell, the production of recombinant alleles, the conditional assembly of genes or generating recombinant livestock as claimed do not result in altering the phenotype of

the ES cell or transgenic animal. Without such a limitation, the methods are not of use in the instant invention. The specification teaches breeding ProCre mice with transgenic mice (page 25-27); however, the ES cells used to make the ProCre mouse did not have a selectable marker construct flanked by recombination target sites as in claims 28-32, 34-43 and 46-51. Nor are claims 28-32, 34-44 or 46-51 limited to the phenotype of the ProCre mouse. The specification teaches transfecting ProCre ES cells with a construct comprising a nucleic acid flanked by two recombination target sites; however, the cells were not brought to term such that one of skill could predict the level of recombinase expression or the phenotype of the resulting animal. Nor does the specification provide any guidance regarding the phenotype that would result in such methods. In addition, the methods do not merely require the "passaging" step claimed. The method may require two breeding cycles and may require a particular sex be used depending upon the type of germline-specific promoter used and what gene is being recombined. In fact, the methods require more than passaging through gametogenesis because the breeding ProCre mice with transgenic mice with two loxP sites did not result in recombination (page 23, lines 17-22). In addition, the phenotypes of the transgenic animals produced in claims 32, 34-44 and 46-51 are not different than wild-type which is the only disclosed use for the methods claimed. Therefore, the claims are not enabled as broadly written.

Claim 43 is not enabled because the specification does not teach any inactive gene segments which can be used to make a eukaryotic cell of interest by merely introducing the segmenting to an ES cell as claimed. It cannot be determined from the specification what steps

and DNA segments are required to obtain a biologically active expression product upon passage of the genome through gametogenesis and conditional assembly of functional genes as claimed.

Applicants argue that the claimed invention has utility as a research tool; however, such a utility is not considered substantial. Using a product for further study is not considered a substantial utility. If using ES cells for further study were the only disclosed utility of the claimed invention, a utility rejection would have been made. However, the enablement rejection is based on the disclosed substantial utility which is to make transgenic animals with altered phenotypes.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 28-32, 34-44 and 46-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-32 and 34-39 are indefinite because the phrase "passaging the genome derived from said embryonic stem cells through gametogenesis" is unclear. It is unclear how a genome is "derived" from an ES cell or how the genome is "passaged" through gametogenesis. It is unclear if applicants intend to claim obtaining an animal from the ES cells and breeding the animal such that the transgene is present in the gametes or whether the transgene is present until gametogenesis, spermatogenesis or oogenesis occurs.

The phrases "to cause excision of the transcriptionally active selectable marker" (claim 28) and "to produce the recombinant allele therein" (claim 35) are intended uses and may not occur; therefore, it is unclear if applicants intend to claim the methods result in excision of the transcriptionally active selectable marker or production of the recombinant allele.

Claims 32 and 34 are indefinite because the phrase "introducing... embryonic stem cells according to claim 12" (claim 32, line 4) is unclear. Claim 12 is directed toward an ES cell, and the introducing step is not in claim 12. Therefore, the introducing step is not according to claim 12. Similarly, claims 35-39 are indefinite because the phrase "introducing... embryonic stem cells according to claim 26" is unclear. Claim 26 is directed toward an ES cell, and the introducing step is not in claim 26. Therefore, the introducing step is not according to claim 26. If applicants intend to claim introducing the ES cells of claim 12 or 26, the claims should be written as such.

Claim 43 is indefinite because the method of conditional assembly does not merely require introducing inactive gene segments into ES cells as broadly claimed. The method does require expression of recombinase because the preamble (lines 1-7) in which recombinase is mentioned is not required in the method steps (lines 8-12) and the phrase "for expression... ... recombinase recombination target sites" (lines 2-6) is an intended use and may not occur. The steps and DNA segments required to obtain a biologically active expression product upon passage of the genome through gametogenesis and conditional assembly of functional genes as claimed cannot be determined.

Claims 49-51 are directed toward "the method" and are dependent upon claim 12. However, claim 12 is directed toward an ES cell. Therefore, the preamble of claims 49-51 does not correlate to the preamble of claim 12. It is unclear if the claims should be dependent on other claims or if the preamble of the claim is incorrect.

Claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51 appear to be free of the prior art of record because the prior art of record did not teach or suggest a mammalian ES cell transfected with a construct comprising a nucleic acid sequence encoding recombinase operatively linked to a germline-specific promoter, wherein the construct is in the genome of the cell and the recombinase is not expressed in the stem cell, a mammalian ES cell comprising a construct comprising a nucleic acid sequence encoding recombinase operatively linked to a germline-specific promoter and a transcriptionally active selectable marker flanked by two recombinase recombination target sites in the genome of the stem cells or methods of using such ES cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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